DEVELOPMENTS IN PROTON AND LIGHT-ION THERAPY

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Abstract

Proton and light ions are used since the middle of last century for the treatment of many tumour sites. These applications are usually known as hadrontherapy treatments. At the beginning most of the patients have been treated in research facilities, where parasitic beams were devoted for relatively short periods to the treatments; only in the nineties hospital based facilities have entered in use. Nowadays proton therapy is a mature field: many firms are competing to offer more and more efficient and reliable proton facilities and also the production of accelerators for light-ion therapy is rapidly increasing. This paper outlines the rationale behind the use of hadrontherapy, summarises the present status of hospital-based facilities in the world with particular emphasis on the Italian facility CNAO under construction in Pave and enlightens the most interesting developments and research aspects.

STATUS OF HADRONTHERAPY

About 90% of the successes in tumour treatments are due to the efficacy of loco-regional treatments: surgery and radiotherapy. The rate of success has much improved in the last decades with the increased capability of early diagnosis due to sophisticated diagnostics tools (CT, MRI, PET, ultrasounds), and with the possibility of eradicating the lesion in a selective way. The use of hadron beams is a step forward in the historical development of more targeted and effective cancer treatments which better spare healthy tissues.

Rationale for Hadrontherapy

Beams of charged hadrons are characterised by the intrinsic capability of depositing the maximum of their energy density in a well defined and controllable location at the very end of their range (the Bragg peak). The penetration depth is determined by the kinetic energy of the particles: 200 MeV protons and 4800 MeV carbon ions penetrate about 27 cm in the body.

The reason to treat patients with fully stripped ions of higher mass (A) and charge (Ze) than protons is linked to the increase in the energy deposition per unit track length (LET = Linear Energy Transfer) that determines an increased radiation efficacy towards the end of the range. It is the higher electron- and consequently ionisation-density that yields a greater effectiveness. The main target of the radiation attack is the DNA inside the cell nucleus. The DNA, essential for our life, is highly protected by an extremely elaborate repair system so that DNA violations, like single or double strand breaks, are rapidly restored. But when DNA is exposed to very high local doses, where local refers to the nanometre scale, the DNA lesions are clustered and the repair system fails. Then the dose is more effective compared to sparsely ionizing radiation and the radiation radio-biological efficacy (RBE) is increased.

Clinical Indications and Running Centres

Relying on the abovementioned rationale, hadrontherapy has been practiced in many centres since the early 1950's, at the beginning in research facilities built for fundamental physics and since the 1990's also in hospital-based facilities conceived with the objectives of treating patients (typically more than 500 per year with at least two treatment rooms) and performing clinical and radiobiological research. A continuously updated picture of the world-wide situation is found on the website (http://ptcog.web.psi.ch/) of PTCOG, the Particle Therapy Co-Ordination Group. The overall number of treated patients with hadrons is continuously increasing. Also the clinical indications are growing (Figure 1).

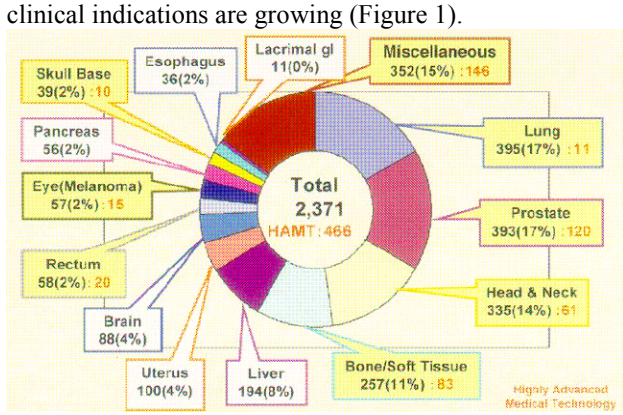

Figure 1: Number of patients and pathologies registered in Carbon ion therapy at Chiba – Period: August 1994 – August 2005 (courtesy of Prof. H. Tsuji - Chiba).

From epidemiological data taken from the various national Registers of Tumours (e.g. [1]), considering 10 million European citizen, it is presently estimated that, each year, 200 of them are affected by a pathology that is electively treatable with protons and that about 2000 would profit, in term of local control, of a protontherapy treatment. Concerning carbon ions, that are still a clinical research issue, at least 600 new patients per year, among the 10 million European citizen, are affected by radioresistant tumours and thus should be entitled to enter in a clinical research trial with carbon ions.

Hospital Based Facilities in the World

The number of hospital based facility for deep protontherapy have increased a lot in the last decade. There are five companies that offer turnkey facilities with multiple treatment rooms. The needed investment is around 70 million Euro. The accelerating machine is either a cyclotron or a synchrotron (diameter of about 7

meters) and both products have reached the reliability necessary to operate in a hospital environment. At present, 5 centres in USA, 4 in Japan, 2 in China, 1 in Switzerland, 1 in Germany, 1 in France, 1 in Korea, 1 in Italy are either running or are financed.

Concerning 'dual facilities', i.e. centre for carbon ions and protons, the situation is different. In Japan firms have been deeply involved in the realisation of the two existing centres (the HIMAC belonging to NIRS at Chiba and the HIBMC at Hyogo). The Japanese firms are not presently active on the European market and only recently some industries have shown their interest in the forthcoming market of heavy-particle therapy. It will be outlined in the presentation of the Italian National Centre for Oncological Hadrontherapy (CNAO from the Italian acronym), that the effort is such that experienced people from research institutions are needed to integrate and to steer the companies in producing the first centres.

A similar facility, the Heidelberg Ion Therapy Centre (HIT), is under construction in Heidelberg (Germany) under the technical coordination of GSI. The first patient treatment is planned for fall 2007 and it is foreseen to equip two horizontal beam lines (for protons and carbon ions), an experimental cave and one room with an isocentric gantry for ions, that is actually unique in the world. A second ion dual therapy centre has been approved in December 2005 in Germany, at the Klinikum Geisse-Marburg in Marburg. In Europe many other projects are at different stages of the approval and financing path, Med-Austron in Wiener Neustadt (Austria) and Etoile in Lyon (France) being the most advanced. The European Network for Light Ion Therapy (Enlight) has been an important meeting point for the national initiatives to exchange and coordinate their activities. In 2006 it has been also decided to extend the collaboration to new partners, to include also common clinical research projects, and to apply for the 7th framework programme (Enlight++).

An Example: the Italian CNAO

CNAO is under construction in Pave, about 30 kilometres South-West of Milan. The Italian Ministry of Health, which, in the year 2001, has created the CNAO Foundation to build and run the facility, mainly finances it. The founders of CNAO are five major hospitals, seated in Milan and Pave, and the TERA Foundation (lead by U. Amaldi who was the promoter of CNAO since 1992). Since 2003, INFN (the Italian National Institute of Nuclear Physics) is Institutional Participant of CNAO, together with the Universities of Milan and Pave, the Polytechnic of Milan and the Town of Pave.

The realisation of CNAO started in September 2002 with the final design of the high technology part. At present it is foreseen to start the operation of the machine and to begin the preparation to treatments in fall 2007. In 2006 about 65 fte engineers, physicists and technicians, of which almost 35 belonging to CNAO Foundation, work on the project and follow and coordinate the activities of more than 80 firms involved in the buildings and the high technology realisation. INFN is deeply involved in the CNAO construction being in charge of the project co-direction ship and participating in the development of 15 tasks.

The CNAO design is based on the following assumptions:

- the Centre will be devoted to the treatment of deep-seated tumours (up to 27 cm of water equivalent) with light ion beams (proton, carbon ions and others) and to clinical and radiobiological research;
- the full-size CNAO will have 5 treatment rooms (3 rooms with fixed beams and 2 rooms with gantries) and one experimental room. For the first phase 3 treatment rooms will be equipped with 4 fixed beams, three horizontal and one vertical (CNAO - Phase 1).

The CNAO building develops on four levels; the underground level hosts the accelerators and the treatment rooms and is shown in Figure 2.

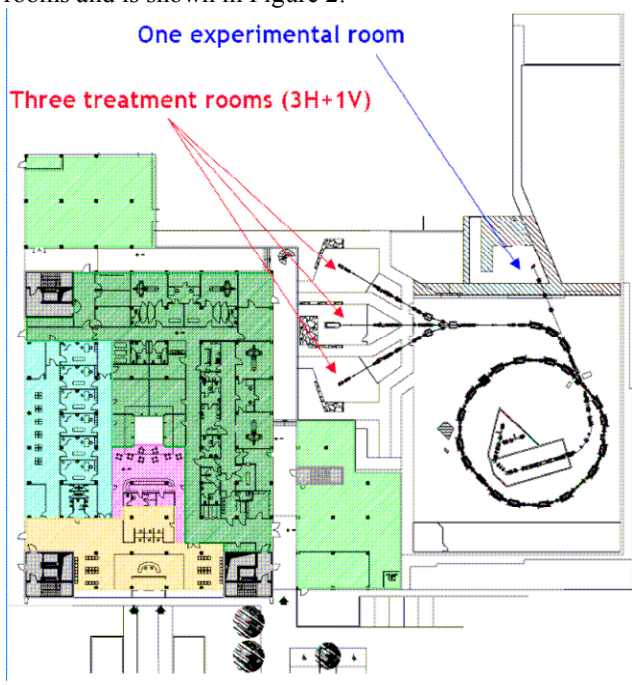

Figure 2: Layout of the CNAO underground level.

The construction of the buildings and plants is ongoing; the first part to be completed is the one devoted to the high technology components (on the right of Figure 2). It will be delivered by October 2006 and then the accelerator installation will start.

The high technology design has been driven by the clinical requirements of the therapeutical beams, specified in Table 1. The basic design of the CNAO accelerator and lines has been hosted at CERN in the frame of the Proton-Ion Medical Machine Study (PIMMS), from 1996 to 1999 [2]. This concept design has been fully engineered, first by TERA and then by CNAO/INFN (with GSI for the Linac, CERN for the septa and the kickers, University of Pave and LPSC/IN2P3 Laboratory of Grenoble for the betatron core). The final design now appears as shown in Figure 3.

Table 1: Clinical performance specs for the CNAO.

Beam particle species	p, C^{6+}, (possibly He^{2+}, Li^{3+}, Be^{4+}, B^{5+}, O^{8+})
Beam particle switching time	≤ 10 min
Beam range	1.0 g/cm^2 to 27 g/cm^2 in one treatment room 3 g/cm^2 to 27 g/cm^2 elsewhere Up to 20 g/cm^2 for O^{8+} ions
Bragg peak modulation steps	0.1 g/cm^2
Range adjustment	0.1 g/cm^2
Adjustment/modulation accuracy	≤± 0.025 g/cm^2
Average dose rate	2 Gy/min (for treatment volumes of 1000 cm^3)
Delivery dose precision	≤± 2.5%
Beam axis height (above floor)	150 cm (head and neck beam line) 120 cm (elsewhere)
Beam size[1]	4 to 10 mm FWHM for each direction independently
Beam size step[1]	1.0 mm
Beam size accuracy[1]	≤± 0.2 mm
Beam position step[1]	0.8 mm
Beam position accuracy[1]	≤± 0.05 mm
Field size[1]	5 mm to 34 mm (diameter for ocular treatments) 2×2 cm^2 to 20×20 cm^2 (for H and V fixed beams)
Field position accuracy[1]	≤± 0.5 mm
Field dimensions step[1]	1 mm
Field size accuracy[1]	≤± 0.5 mm

[1] At isocentre or, for fixed beam, at normal treatment distance.

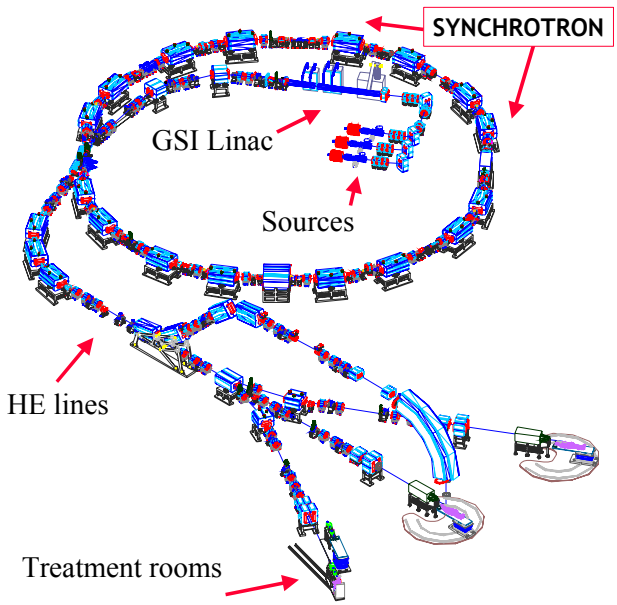

Figure 3: Layout of the CNAO accelerators and beam transport lines. The figure already shows the possibility to add a third source.

CNAO will start activity with two identical ECR sources. The first source has been already produced and preliminary acceptance tests have been performed at the factory. Shipping of the two sources at CNAO is foreseen by November 2006. The layout of the LEBT (Low Energy Beam Transfer) lines is designed in order to switch from one source to the other on a pulse to pulse basis. The linac is composed of an RFQ and an IH-structure coupled together. It is identical to the one built for the HIT project and it is being built under the technical supervision of GSI. This arrangement is very compact and allow the insertion of the sources, LEBT and linac inside the synchrotron ring. The RFQ accelerates particles from 8 keV/u to 400 keV/u, it is presently at GSI and will be tested this summer with the final power amplifier. The IH will be ready in fall 2006. It accelerates the beams from 400 keV/u to 7 MeV/u.

The Medium Energy Beam Transfer line (MEBT) transports the beam from the stripping foil to the injection point in the synchrotron. In MEBT a final selection of the ion specie is made to avoid beam contamination and the current injected into the ring can be adjusted by a factor 10 (to cope with intensity variations at the patient, another factor bigger than 10 is possible at the extraction of the synchrotron).

The CNAO synchrotron is made by two symmetric achromatic arcs joined by two dispersion free straight sections. The dispersion free sections host the injection/extraction region, the resonance driving sextupole and the RF cavity. The total length of the ring is approximately 78 m and accelerates particles till a maximum energy of 400 MeV/u, with a repetition rate of 0.4 Hz. The magnet production is ongoing and Figure 4 shows the prototype successfully tested and measured, in May 2006, at CERN.

Figure 4: The dipole of the CNAO synchrotron.

The vacuum chamber, the beam diagnostics, the power supplies, the RF cavity, the special magnets and the betatron core are in construction and some already tested, accepted and shipped to Pave.

The four HEBT (High Energy Beam Transfer) lines transport the extracted beam to the three treatment rooms. The dipole magnets are identical to the synchrotron magnets and this increases flexibility and reliability, reducing costs. The compact design is based on a switching magnet that is selecting the horizontal line to be used for treatment. Before the end of the HEBT a redundant monitoring station is inserted that measures twice the intensity, the profile and the position of the pencil beam during the active irradiation of the target. It is worth mentioning the central role of the control system. A basic choice has been the selection of commercial and well established products as building blocks of the four levels architecture of the system.

In this short presentation only the technological aspects of the accelerators have been touched. Of course they are closely interlaced with the medical, the medical physics (e.g. patient positioning, medical imaging, treatment planning, dosimetry), the authorisation and organisational aspects that are underway, but have not been mentioned here.

RESEARCH AND DEVELOPMENTS

This section describes the R&D aspects, linked in a broad sense to the accelerator technologies, which appear more interesting and capable of introducing remarkable improvements in the field of hadrontherapy.

Adaptive Radiotherapy: 6D Conformation

The active scanning system implemented at GSI [3] and foreseen also at CNAO, permits a very high degree of precision in the delivery of the dose to the target volume.

This 3D geometric conformation can be expanded integrating in the system other 3 degrees of freedom, that still are the object of R&D programmes: the choice of the best ion species (radiobiological optimization), the tracking of moving organs (tracking optimization) and the availability of a 4π selection of the irradiation direction (gantry optimization).

The radiobiological optimization is an important parameter to be mastered in order to tailor at best the treatment to the specific tumour kind [4]. The availability of multiple ion sources connected to the most performing delivery systems have to be taken into account designing the accelerator chain, as it is the case of CNAO.

The tracking optimisation concerns the capability to follow the target movements, linked to respiration and other physiological movements. At Chiba, the synchronisation between patient breathing and beam extraction is already active by using an infrared (IR) light fixed on the patient thorax and monitored by a camera. The tracking of moving organs is an important issue also for the most advanced conformal radiotherapy with X-rays (IMRT = Intensity Modulated Radiation Therapy) and many efforts are put by medical companies in this domain: external markers with IR cameras, on-line CT scans, ultrasounds are among the latest devices.

The last degree of freedom is the most open to the use of novel accelerator technologies: the introduction of a simple, reliable and cost-effective gantry to direct the ion beam from any direction around the patient. At present the only example of gantry for ions is the one to be installed at HIT. The characteristics of this device (diameter = 13 m, length = 25 m, weight = 600 tons, power consumption = 600 kW) have a large impact on the facility layout, on the running and capital costs. Research programmes have been initiated to study the possibility to use superconductivity, in particular for the last huge 90° bending magnet. Anyway the problem has to be tackled considering the gantry as a system in which mechanics issues (e.g. 360 vs 180 degrees of rotation), technological aspects (superconductivity or else), integrated scanning capabilities (upstream or downstream the last bending) and patient positioning have to be considered and optimised all together.

Novel Accelerator Concepts: Medical FFAG

The Fixed Field Alternating Gradient synchrotron concept dates from the early 1950's. Strong activity on FFAG was started in the last decade mainly in Japan at KEK [5] with the aim to adapt this technology to the production of very large current of high-energy protons. Recently the design of a compact accelerator for heavy ion radiotherapy has also been investigated in spite of the fact that in this case very small currents are needed [6].

This feature derives from the working principle of this kind of synchrotron that uses a fixed value of the bending field. The beam accelerates in a constant field and spirals outward while increasing its energy. The transverse stability is assured by alternating the sign of the bending fields along the beam path, thus realising a strong focusing configuration; of course the net bending power guarantees a circular trajectory.

Present design studies pursue the objective of accelerating carbon beams up to 400 MeV/u, with repetition rate of 200 Hz, with compact, high intensity and cost-effective FFAG structures.

Novel Accelerator Concepts: IDRA

In the field of protontherapy the idea of combining the possibility to produce radioisotopes for tumour imaging and to perform protontherapy appears interesting. This possibility is envisaged by the project named IDRA (Institute for Diagnostics and RAdiotherapy) pursued by the TERA Foundation [7]. The dual modality is realised combining a relatively low energy commercial cyclotron (30 MeV and intensities ranging from tens of μA to almost 1 mA) for radioisotope production, with a linac that boosts a fraction of the beam to energies suitable for the treatment of deep seated tumours (maximum proton energies 250 MeV). The combined chain of two accelerators is called "Cyclinac".

The linac booster (LIBO) has been prototyped by TERA [8] and operates at a frequency of 3 GHz, never experimented before for proton acceleration, but common in hospital environment where conventional linacs are used to produce electron beams up to 20 MeV. An interesting evolution of the LIBO concept is represented by a patented linear structure called CABOTO (CArbon BOoster for Therapy in Oncology) [9] that would be suited to boost a carbon beam produced by a limited range carbon ion accelerator.

Imaging: Quality Assurance

An important advantage of particle beams is the 'in situ' production of positron emitters like carbon 10 and 11 and oxygen 15. Because the stripping of one or two neutrons is a minor perturbation, the residual carbon ions after the break-up continue their flight and form a maximum of β+ activity close to the Bragg peak of the stabile carbon ions. By monitoring the positron emitting isotopes by a PET camera during and shortly after the beam application the actual stopping points of the beam can be controlled [10]. R&D projects concerning the "on-beam PET" are ongoing in many directions. First of all the choice of the photons detectors: crystals are the present choice, but gas detectors could present advantages and more flexibility to cover a larger solid angle around the target. It would be very useful to have the possibility

to check the Bragg peak localisation at the beginning of each session just delivering a small fraction (10%) of the dose. The last and final goal is the development of a quantitative measurement of the effective dose delivered to the patient through PET reconstruction.

Imaging: Tumour Targeting

For the achievement of an adequate accuracy of tumour localisation, imaging techniques have become crucial for clinical practice. Assessment of the molecular and functional features of tumours by means of PET may allow the definition of local features that can be exploited in order to focus the treatment strategies.

About 200 medical radioisotopes accelerators are presently running in the World, mostly cyclotrons. These devices are sufficiently safe, reliable and efficient to operate close to the medical departments, but every technological improvement that could simplify, or even introduce alternatives to the production-distribution chain of radioisotopes is obviously welcome. Recent developments of the Plasma Focus technology, known since the early 1960's appear promising. The working principle consists in inducing nuclear reactions in a limited region of plasma (20-300 μm) constrained by strong magnetic forces, where very high densities and very hot temperatures (above 3 keV) are reached. The proper choice of the filling gas induces the generation of PET radioisotopes, like ^{18}F, ^{15}O, and the production is not accompanied by neutron emission that normally imply severe radioprotection issues. The PFMA-1 (Plasma Focus for Medical Application) has been prototyped [11], but the goal to breed 1 Ci of ^{18}F in two hours of production, in a hospital-based environment, is still to be demonstrated.

Long Range Perspective: Laser Sources

Sub-picosecond laser pulses of hundreds of terawatt have extracted from a thin target a continuous spectrum of protons having energies as large as 60 MeV [12]. Particle In Cells (PIC) calculation have show that 200-300 MeV can be produced with 10% monochromatic beam if a metallic double layer target is used and the laser power is about 1 petawatt (i.e. 50 joule in 50 fs) and is focussed on a spot of a few micron diameter [13]. This is promising because the laser beam would be easily transportable with a mirror array to a target located close to the patient. It has to be underlined that the repetition rate and energy spectrum are of major concern for medical applications.

To finish, a short remark on the use of antiprotons. The production of antiprotons requires expensive accelerators and thus has to be centralized in big facilities. The cost is large and uncertain. A basic issue to be clarified concern the high energy released by a single antiproton at the end of the range due collisions and to the annihilation processes. The short 'dark' tracks have a high LET (and RBE), but the number of antiprotons required to deposit a few grays is correspondently reduced together with the number of DNA traversals. This phenomenon could produce microscopic cold spots on clonogenic tumour cells causing the tumour to reoccur after treatment and requires detailed investigations.

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